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THE REPRODUCTIVE TOXICOLOGY OF PESTICIDES

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16. ABSTRACT

A review of tests used to evaluate reproductive toxicity and the application of such methodologies to the evaluation of the potential of pesticides to induce developmental and/or reproductive toxicity will be presented. Reproductive toxicity encompasses adverse effects on the male and female reproductive systems, teratology, and perinatal toxicity. Examples of adverse effects of pesticides on mammalian systems will be given as shown in multigeneration and teratology studies as well as tests designed to specifically identify the sites of injury to the reproductive system. Problems in the interpretation of such data will be illustrated by the studies which are discussed and suggestions for the improvement of test approaches are given.

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The successful reproduction of any species depends upon the accurate and orderly integration of genetic, biochemical, physiological, developmental, and functional processes. Any significant interference with the normal functioning of the organism may manifest itself as an adverse effect on reproduction. While this statement is an extremely obvious one, it is important to bear in mind given the design and endpoints of some of the standard protocols used to assess reproductive toxicity. If we strictly define the processes which are essential for mammalian reproduction we may list the following components: genetic integrity; gametogenesis; transportation of the gametes; fertilization; formation of the pre-implantation embryo; maternal hormonal, physiological, and structural alterations necessary for in utero development; implantation of the embryo; placentation; embryogenesis; fetal growth; parturition and the changes necessary for the fetus to assume an independent existence; maternal/neonatal relationship; and postnatal growth and maturation. In a practical (or regulatory) sense, reproductive toxicity is divided into two areas: the potential of agents to adversely affect either structural or functional development (teratogenicity), or any of the other processes listed above (reproductive toxicity).

Prior to any review of the relevant literature, a brief dission of the standard protocols utilized to determine reproductive toxicity is desirable. Generally, reproductive toxicity is evaluated by variations on one of three types of bioassays dealing respectively with 1. general fertility and reproduction in which animals are exposed to the agent and the viability and the fertility of the offspring are measured (multigeneration study); 2. a test in which the agent is administered to the pregnant animal and fetal anomalies are recorded; (teratology or developmental toxicology study); and 3. a study in which animals are exposed to the test compound late in gestation and through the lactational period (perinatal study).

The multigeneration study consists of multiple dose groups and concurrent controls which receive the test substance through a premating period that covers both the spermatogenic and estrus cycles of the animals (generally the rat, although other rodent species have been used). The precise design of the study depends upon the country it is done in and varies from a fertility study in which the compound is administered only through the early gestational period (Japan) to a multigeneration study (as is done in the U.S.A. and Great Britain). There has been considerable debate concerning both interim sac-

rifices of pregnant females during gestation, and the need for more than one or two generations (Clegg, 1979). Generally a minimum of two litters for each generation is recommended and in some protocols histopathology is done on offspring of the last generation. A detailed listing of the designs of the different protocols currently in use can be found in the ECETOC (1983) document. There has been considerable discussion of the benefits of the different experimental designs used in multigeneration studies (Palmer, 1981; IPCS, 1984; Christian, 1986) and there has been, in recent years, some movement towards concurrence of the basic design - one which omits the third generation and the interim sacrifice of females for examination of their litters. I would like to emphasize the following point: the multigeneration study as it is presently constituted does not identify agents that adversely affect the reproductive system in a strictly defined sense. These studies are perhaps more properly thought of as tests of the bioactivity of agents across generations. Sick animals may lose their ability to breed by innumerable factors not directly dealing with any of those listed above as part of the continuum needed for successful reproduction. Similarly, a positive finding in this study often revolves about the loss of pups but unless we are aware of damage to the reproductive system itself all that we know is that the agent being tested has caused some severe adverse effects that have manifested themselves in death of the offspring.

There have been a number of symposia and articles in recent years which have focused upon the need for test protocols that will identify specific reproductive system components that may be the targets of xenobiotics. Among the parameters that have been suggested to accomplish this aim are the identification of estrogen and androgen agonistic-antagonistic activity; dysfunctions in the hypothalamic-pituatary-gonadal axis; alterations in reproductive behavior; ovarian toxicity; inhibition of steroidogenesis, alterations in seminal fluid composition; and various measures on critical parameters of sperm including numbers, morphology, motility, and ability to fertilize. The identification and validation of suitable tests to evaluate these aspects of the reproductive cycle will enable both the identification of compounds capable of selectively affecting reproductive parameters and the specific sites of injury (E.P.A. 1980; Dixon and Hall, 1982).

The protocol utilized for the assessment of an agent's potential to affect embryo/fetal development involves the exposure of pregnant animals to

the test compound throughout the period of major organogenesis, gathering the fetuses shortly before parturition, and the subsequent examination of the fetuses for both soft tissue and skeletal anomalies. Generally two species are called for, and multiple dose levels are used - one of which is high enough to induce some form of overt maternal toxicity. Examples of such protocols may be found in a number of sources including the Canadian (1977), OECD (1981) and the EPA (1982). There are some basic limitations of the standard protocol which should be noted. The fetal examination is entirely morphological and therefore may both miss subtle or small defects in organs. and fail to identify either critical organ toxicity in the fetus or biochemical defects that may only manifest themselves as postnatal functional deficits. The utilization of dose levels which induce maternal toxicity raises the question of the potential of such toxicity to affect the embryo/fetal response in a general fashion. Related to this last point is the question of the potential role that compound-induced maternal nonspecific stress may play in the production of fetal anomalies.

Recent work has indicated that the concerns raised above may indeed be significant factors in our assessment of teratology data. Kavlock et al. (1982) have shown that compounds are capable of affecting critical biochemical parameters of selected fetal organs at dose levels below those required to elicit gross morphological alterations. That there are numerous chemicals which produce in utero effects manifesting themselves as postnatal functional deficits is becoming clear with the work of many researchers who have investigated the functions of a variety of organ systems during the postnatal period. Abnormal functional development resulting from in utero exposure has been identified in the cardiac, renal, pulmonary, central nervous, and other systems (see Kimmel and Buelke-Sam, 1981; and Kavlock and Grabowski, 1983). The relationship(s) of maternal and embryo/fetal toxicity has been examined by both literature review and experimentation. Khera has found an association between specific types of anomalies and the presence of overt maternal toxicity in standard teratology tests published in the open literature (Khera, 1985) although the work of Kavlock et al. (1985) on acute maternal toxicity and fetal development indicated only chemical specific effects with the exception of an increased incidence of supernumerary ribs raising the question of effects of general maternal stress on the production of birth defects. Adverse embryo/fetal effects have been noted in litters of dams subjected to various forms of stress including noise (Nawrot et al., 1981) and restraint

(Barlow et al., 1975;). The results in these studies have varied with the form of stress and the species used. Recent work has shown that restraint stress produces supernumerary ribs encephaloceles, and fused ribs in mice but is without effects in rats (Beyer and Chernoff, 1986). The degree of stress as measured by appropriate biochemical parameters has not been measured in any studies done to date so no definitive statements can be made concerning possible comparisons between the stresses used above and those produced by toxic levels of xenobiotics. The above work points out that we must interpret the standard teratology protocol carefully and in many cases, especially where we have overt maternal toxicity and/or no postnatal information, additional studies are needed as predicated by the data generated.

The third type of test, a perinatal study, involves dosing during late gestation through the lactational period. As Palmer (1981) points out, such studies may serve to identify those compounds whose effects take place during this period rather than seeing such effects as part of the more expensive and laborious multigeneration study. Such studies are not universally called for, and it might be useful to attempt to form a consensus on their need and design. It has been suggested that some form of postnatal study be a part of every standard teratology test thus enabling investigators to identify effects that are not readily apparent with fetal examination as well as to obtain information on the significance of a variety of fetal effects that are difficult to interpret in a regulatory setting (e.g. supernumerary ribs, enlarged renal pelvis, and reduced fetal weight). The above discussion should serve as an introduction to a general review of the potential of pesticides to adversely affect the reproductive cycle of mammals. It is beyond the scope of this paper to detail all of the numerous studies that have been published on this subject, and my intent is to examine a selected body of data to illustrate the variety of pesticides found to have adverse reproductive effects, as well as the types of tests which have been used to show such toxicity.

There have been numerous multigeneration studies performed on pesticides, the majority done to comply with regulatory needs. Examples of this type of study include those done by Collins et al. (1971) on the insecticide Carbaryl. These experiments followed standard U.S.A. Food and Drug Administration protocols for three generation reproductive toxicity studies.

These scientists found a significant weight reduction in treated pups at all dose levels. At the two highest dose levels the authors noted impaired fertility, and dose-related decreases in litter size, number of liveborn, and postnatal viability. Finally, there was a significant growth depression seen in maternal animals at the highest dose level. Murray et al. (1979a) studied the reproduction of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) which may be a contaminent of compounds made from 2,4,5-trichlorophenol including the herbicide 2,4,5-trichlorophenoxyacetic acid. They found that administration of this chemical to rats across three generations produced adverse reproductive effects as seen in reduced fertility, litter size, and postnatal growth. These effects are similar to those noted in an earlier study by Khera and Ruddick (1972) in which TCDD was administered to pregnant rats during gestation days 6-15 and indicate that TCDD causes fetal death and perinatal growth retardation. The studies reviewed above indicate their utility in the determination of the biological activity of the compounds studied. They give clear evidence that these compounds interfere with normal biological functioning at some dose levels, but it should also be noted that there is no evidence of selective effects on any reproductive parameter. Whether the effects noted by both Collins et al. (1971) and Murray et al. (1979) are due to general toxicity or selective effects on components of the reproductive system remains unknown. The multigeneration study in concert with other tests of chemicals' biological activities allows us to make rational assessments on their potential health effects, and may serve to direct the course of further tests. For information on the reproductive system itself, other studies especially designed to evaluate specific components of this system may be necessary.

The critical role that estrogens play in the reproductive cycle is well known and pesticides that have estrogenic properties have been demonstrated to affect reproduction. Those pesticides have been shown to directly affect the female reproductive system include DDT, chlordecone, methoxychlor, and mirex. Heinricks et al. (1971) administered o,p'-DDT to pre-pubertal rats and showed that treated females exhibited precocious puberty, increased uterine weight, and persistent vaginal estrus. Chlordecone induces defeminization, and persistent vaginal estrus when administered to rats during the period of behavioral differentiation (Gellert, 1978). Similarly, Gray (1982) showed that the administration of chlordecone to neonatal hamsters results in masculinization of females resulting in persistent aberrant sexual behavior. Dietary

exposure of methoxychlor to rats before mating resulted in early vaginal opening and reduced reproduction in female offspring (Harris et al., 1974). The relatively few pesticides which have been shown to directly affect the male reproductive system are generally chlorinated hydrocarbons with estrogenic properties. Whether the relative lack of compounds shown to adversely affect females reflects the relative ease with which the male reproductive system may be studied, or the relative insensitivity of the female system is not known at this time.

Numerous pesticides have been shown to significantly alter male reproductive parameters in laboratory studies. As would be expected, compounds which exhibit estrogenic properties may affect both female and male reproductive parameters. DDT exposure in male dogs results in decreased reproductive capacity (Deichmann et al., 1971), reduced uptake of testosterone in the prostate in mice, and o,p'-DDT has been shown to affect androgen metabolism in man (Hellman et al., 1973). The adverse effects of chlordecone on the male reproductive systems in laboratory animals as well as workers exposed to large quantities of this pesticide, have been well documented. Exposure to this pesticide in adult rats resulted in transient decreases in both viability and motility of epididymal spermatozoa along with decreased sperm reserves in the cauda epididymus (Linder et al., 1983). Male workers who were exposed to large amounts of chlordecone during the manufacture, exhibited adverse central nervous system, course of its hepatic, and reproductive effects. The effects on sperm were similar to those later shown in laboratory studies and included decreased counts and motility as well as an elevated incidence of abnormal morphology (Taylor et al., 1978). The cyclodiene pesticides dieldrin (Schein and Thomas, 1975) and chlordane (Levin et al., 1969), and the herbicide 2,4,5-trichlorophenoxyacetic acid (Lloyd et al., 1973) have all been shown to alter testosterone kinetics but the effects (if any) on reproductive function remain unknown. The organophosphate dichlorvos has been tested in rats (Krause and Homola, 1974) and histopathological examination revealed degeneration of the seminiferous tubules accompanied by significant reductions of spermatozoa and spermatids. The bipyridal herbicides diquat and paraquat were found to induce significant adverse effects on the development of sperm when administered to mice (Pasi et al., 1974). Prenatal treatment with the diphenyl ether herbicide nitrofen early in gestation results in anomalies in the male reproductive tract while treatment later in gestation produces behavioral alterations and reduced fer-

tility in male offspring (Gray et al., 1985). The dinitrophenol herbicide dinoseb has been shown to induce severe morphological alterations in sperm coupled with significant oligospermia when the compound was administered to the rat in the diet (Linder et al., 1982). The fumigant ethylene dibromide produced oligospermia and degeneration of existing spermatozoa in bull calves fed the pesticide for a year following birth (Amir and Volcani., 1967). Another fumigant, 1,2-dibromo-3-chloropropane (DBCP) has been shown to produce adverse male reproductive effects in both laboratory animals and in exposed humans. Testicular atrophy has been documented after inhalation exposure in rats (Rao et al., 1983). This pesticide also produced reduced fertility in occupationally exposed workers, and testicular biopsies in affected individuals indicated significant oligospermia (Whorton et al. 1979). The fungicide benomyl has been shown to exhibit age-related male reproductive toxicity. The oral administration of this pesticide in the pubertal or postpubertal rat results in decreased testicular weight, and decreased sperm in the epididymus and vas deferens. Similar administration in the prepubertal animal did not induce these alterations (Carter et al., 1984).

A recent review by Schardein (1985) listed approximately 200 pesticides or their degradation products as having been tested for their teratogenic potential. Of these, some 90 were indicated as having one or more studies which have resulted in positive teratogenic effects under the experimental regimens used. There are to date, however, no well documented associations between the human exposure to pesticides and the subsequent occurrence of birth defects. This apparent disparity between positive effects noted in animals studies and the lack of known human effects, is similar to the general situation with the teratogenic potential of all types of agents, and it should be noted, for other aspects of reproductive toxicology. Shepard (1986) estimates that some 900 agents listed in his catalogue have been shown to produce birth defects in the laboratory setting while only between 20 and 30 agents are known to be teratogenic in humans. These differences in response(s) may have a number of basic causes. Interspecies differences may be the result of differences in maternal metabolism and/or sensitivity, embryo/fetal developmental patterns, and placentation. The major contributor to the apparent interspecies difference is most probably the fact that virtually all standard teratology bioassay protocols used to register pesticides utilize a high dose which induces some form of overt maternal toxicity so as

to maximize the chances of seeing an effect with a small number of animals. These dose levels are invariably far greater than that which would be encountered by humans during appropriate environmental exposure. When the results of such studies are considered in a "margin of safety" framework, they provide for a scientifically reasonable approach to the protection of the human population. It should be noted that for an agent to be firmly identified as a human teratogen, a number of practical criteria may have to be met. The agent has to either produce a large increase in defects which would be noted by alert health personnel as in the case of rubella (Gregg, 1941), or a type of defect of such an unusual nature that it would again be noted by health personnel such as was seen with thalidomide (McBride, 1961). The epidemiological identification of a specific pesticide which produced a relatively small increase in a variety of common birth defects would be extraordinarily difficult to achieve given the complexity of the human environment.

The following review of the teratogenicity of pesticides will, of necessity, will concentrate on commonly used pesticides, and those which illustrate some of the problems alluded to above. The carbamate insecticide carbaryl has been extensively studied by many workers in a range of species including the rat, mouse, guinea pig, rabbit, and dog (see Cranmer, 1986). Adverse embryo/fetal effects were seen in a number of these species including fetal death in the rat and rabbit, skeletal defects in the guinea pig, and a broad spectrum of severe defects in the dog including agenesis of the external genitalia, pubis and ischium, and various viscera. When these data are examined a pattern is seen which indicates that these defects were only noted at dose levels at which overt maternal toxicity was present. The maternal toxicity included lethality, decreased weight gain, clinically observable cholinesterase inhibition, and dystocia. These data indicate that the developing organism is not especially sensitive to carbaryl, but rather, that the doses required to elicit developmental toxicity are similar to those resulting in maternal toxicity and are far in excess of any that might be encountered in the environment. It has generally been concluded therefore, that although carbaryl is known to be fetotoxic/teratogenic in a number of species it does not present an unreasonable risk to pregnant humans in the general population under approved patterns of use.

The cyclodiene insecticide endrin produced neural defects in the ab-

sence of maternal toxicity after single administration on day 8 in the hamster (Ottolenghi et al., 1974). When the compound was administered during the standard period, days 4-15 (Chernoff et al., 1979), the neural defects noted in the former study were only noted at dose levels that were maternally toxic. Kavlock et al., (1981) studied the teratogenic potential of endrin in mice and their studies indicated that in this species also, fetal toxicity was present only at maternally toxic dose levels. Here too, as in the case of carbaryl, embryo/fetal and adult toxic dose levels are similar when standard periods of prenatal administration are used.

The herbicides 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4-dichlorophenoxy acetic acid (2,4-D) are widely used and have been extensively tested for their teratogenic potential. Early work which found significant increases in fetal toxicity in rats and mice (Courtney et al., 1970) may have been confounded by the presence of significant levels of 2,3,7,8-tetrachloro-di-benzodioxin (TCDD). Studies with the purified herbicide have shown that at dose levels approaching maternal toxicity, 2,4,5-T is fetotoxic in the rat (Sparschu et al., 1971). In the mouse, Neubert and Dillmann (1972) demonstrated that this compound produced reductions in fetal weight and cleft palate. Nelson et al. (1979) reviewed the epidemiological data on this chemical and reported on such a study that they had performed. They concluded that there was no demonstrable relationship(s) between the incidence of birth defects and exposure to 2,4,5-T. The closely related herbicide, 2,4-D has been found to produce fetotoxicity in rats including wavy ribs, edema, and delayed ossification (Schwetz et al., 1971).

The fungicide benomyl is teratogenic in both the mouse and rat, producing a wide spectrum of malformations when it was administered by oral gavage. The administration of benomyl via dietary exposure was an order of magnitude less effective in producing fetal effects when maternal intakes on a mg/kg/day basis are compared (Kavlock et al., 1982). This study illustrates the potential importance of the route of administration in the determination of fetal outcome after exposure to an agent. Captan has been widely studied in large part because of its structural relationship to the potent human teratogen, thalidomide. Results to date have indicated that this chemical is not teratogenic in rabbits (Fabro et al., 1966) or rats (Kennedy et al., 1968). Maneb is a dithiocarbamate fungicide that has been found to be teratogenic in rats (inducing hydrocephaly) but not in the mouse or hamster. These re-

sults parallel the effects seen after exposure to ethylene thiourea, a primary degradation product, in these species (Chernoff et al., 1979).

There has been, in recent years, an increasing tendency of teratologists to examine postnatal animals for signs of prenatally induced injury. Such studies have indicated that postnatal evaluations often yield information not readily obtained during the course of standard fetal examinations. The prenatal administration of the herbicide nitrofen results in ablation of the Harderian gland, an effect which cannot be identified during fetal examination (Gray et al., 1983). In the case of benomyl (discussed above) it is of note that the most sensitive indicator of perinatal exposure was a permanent reduction in testes and accessory gland weights Kavlock et al., 1982). Examination of postnatal animals treated with the insecticide mirex has revealed that this compound induces cataract formation with in utero (Rogers and Grabowski, 1984) or neonatal exposure through the maternal milk (Scotti et al., 1981), an effect not readily noted during fetal examination.

In this paper I have attempted to give an overview of the reproductive toxicity of pesticides. I have tried to illustrate the wide variety of effects that have been noted in the laboratory setting, as well as in those few instances where deleterious human effects have been conclusively shown. I have also attempted to utilize compounds and/or studies which highlight some of the common problems facing regulatory personnel in their attempts to extrapolate laboratory studies to human populations - questions of relevance of effects, appropriate routes of administration and dose levels, interspecies differences, and limitations inherent in the commonly used protocols.

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